Longitudinal study on cat allergen exposure and the development of allergy in young children

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Background: The influence of cat allergen exposure in early childhood on the development of sensitization and allergic diseases is complex. Little is known about the natural course of the sensitization development within individuals.
Objective: We investigated the association between cat allergen exposure in infancy and cat ownership and cat contact during childhood and the development of cat sensitization and allergic diseases up to age 6 years using a longitudinal analysis approach.
Methods: Overall, 2166 children from an ongoing birth cohort study were included in the analysis. House dust samples were collected 3 months after birth. Cat allergen levels were extracted. Blood samples were collected when the children were 2 and 6 years old. Information on the allergic symptoms of children and doctor-diagnosed allergic disease were collected at each follow-up using questionnaires.
Results: Cat allergen exposure in infancy was positively associated with sensitization at age 2 years but not at age 6 years. No associations existed between cat allergen exposure in infancy and allergic symptoms and diseases up to age 6 years. Cumulative allergen exposure from cat ownership and regular cat contact increased the risk of cat sensitization up to age 6 years.
Conclusion: Cat allergen exposure in infancy increases the risk of sensitization development in early childhood but not in school-age children. Cumulative allergen exposure from cat ownership and regular cat contact during childhood contribute to sensitization development up to school age.
Clinical implications: Cat allergen avoidance at home alone might be not effective to prevent the development of allergic sensitization in young children. (J Allergy Clin Immunol 2007;119:1148-55.)

Key words: *Allergy, cats, children, cohort study, house dust, ownership, sensitization*

Environmental and occupational respiratory disorders

The influence of cat allergen exposure in early childhood on the subsequent development of sensitization and allergic symptoms and diseases is complex and controversial. Prospective cohort studies have reported positive associations between cat allergen exposure in infancy and increased specific immunoglobulin E to cat allergen during childhood.[1-3] Cross-sectional studies have also found increased cat sensitization rate in children who live with cats.[4,5] Other studies suggested that cat ownership during the first year of life is protective against the development of allergic sensitization.[6,7] These results correspond to the speculation of the induced immune tolerance via IgG_4 antibodies production[8] and the proposed assumption that pet keeping may increase the exposure to bacterial components such as endotoxin,[9-12] which may enhance young children's type 1 lymphocyte (T_H1) development and therefore protect them from allergic sensitization.[13] This observed protective effect, however, may be partly from selective cat avoidance by atopic parents.[14-16] Although recent prospective cohort studies have shown consistent positive associations,[1-3] the role of childhood cat allergen exposure for the development of allergic disorders is still disputed.

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Abbreviations used
Fel d: *Felis domesticus*
ICC: Intraclass correlation

In most studies, health outcomes were only determined at one time point. The pattern of allergic sensitization and symptoms is known to change with age. Sensitization to food allergen starts in early infancy, whereas sensitization to cat dander and other inhalant allergens is more frequent at preschool and school age. However, sensitization to perennial inhalant allergens in early childhood was found to be associated with a loss of lung function in school age.[17] Little is known about the natural course of the development of sensitization and atopic disease within the individual. Previous cohort studies have not analyzed sensitization development using a longitudinal statistical analysis approach.

The aim of this study is to investigate the association between cat allergen exposure in infancy from mattress dust and continuous cat allergen exposure from cat ownership and cat contact during childhood and the development of cat sensitization and allergic diseases using a longitudinal analysis approach and to describe the subsequent course of cat sensitization development up to 6 years of age.

METHODS

Study population

The Lifestyle–Immune–System–Allergy (LISA) study is an ongoing birth cohort study of the influences of lifestyle-related factors on the immune system and the development of allergies in childhood. Detailed description of screening and recruitment has been provided elsewhere.[18] Briefly, parents of neonates admitted to maternity hospitals in Munich, Leipzig, Wesel, and Bad Honnef, Germany, were contacted. Overall, 3097 neonates were recruited into the study between December 1997 and January 1999. LISA is designed as a population-based study, and the participants were not preselected based on family history of allergic disease. In the Munich and the Leipzig subgroup, the house dust samples were collected. The cohort was followed up at the age of 6 months, 12 months, 18 months, 2 years, 4 years, and 6 years. The study was approved by the ethics committees of Bavarian General Medical Council and the University of Leipzig. In the current article, only 2443 children who have been recruited from Munich and Leipzig were included in the analysis. The detailed description of the Munich and Leipzig subcohort has been provided in previous publications.[19,20]

Questionnaire data

Information on parental educational level, family history of allergic disease, infection in pregnancy, smoking in pregnancy, and breast feeding were collected using self-administered questionnaires at and 1 year after birth of the cohort. Information on the allergic symptoms of children; doctor-diagnosed asthma, eczema, and hay fever; cat ownership; contact with cats outside home; and moving home were collected at each follow-up using self-administered questionnaires. The question ''(In the past 6 months/2 years,) did your child have regular contact with any of the following animals outside the house cat?'' was used to assess any regular contact with cat in the nondomestic settings when the children were 3, 12, and 18 months and 2 and 4 years old.

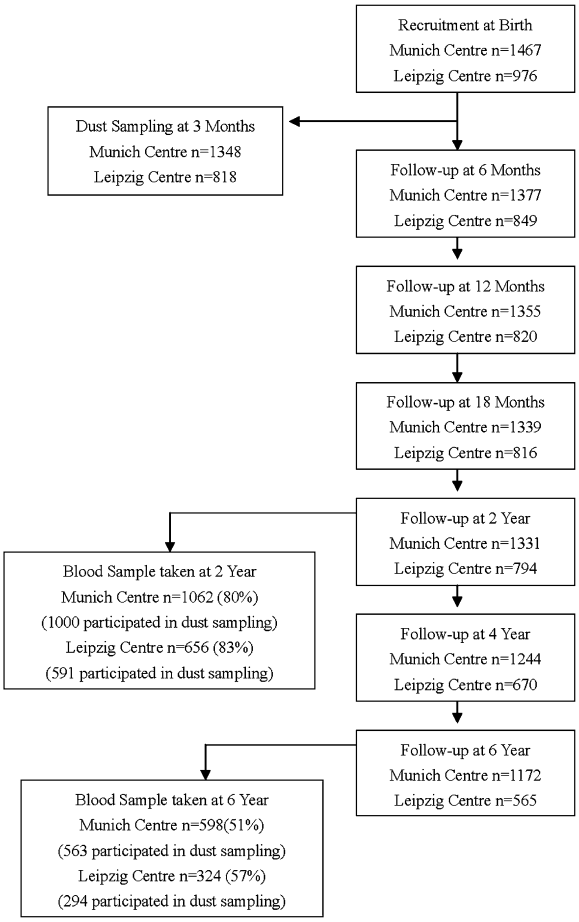

FIG 1. Consort diagram of the LISA study, Munich and Leipzig subgroups.

Collection and analysis of blood samples

With parental consent, blood samples were collected from 1591 (65%) and 857 (35%) children when the children were 2 and 6 years old, respectively (Fig 1). Specific IgE antibodies to cat allergens were measured using the RAST FEIA CAP system (Pharmacia, Freiburg, Germany). Sensitization was defined as having a specific serum IgE titer greater than 0.35 kU/L to cat allergen.

Collection and analysis of house dust

The house dust samples were collected when the children were 3 months old. A total of 2166 (89%) families recruited from the Munich and Leipzig centers participated. Trained field workers carried out dust sampling based on a standardized operating procedure.[21,22] Dust samples were taken from parent and children mattresses by vacuuming 1 m^2 of the mattress surface for 2 minutes using vacuum cleaners equipped with special nozzles (ALK-Abelló allergen mouthpiece, Hørsholm, Denmark). The samples were stored at –20°C until extraction to prevent bacteria growth. The dust samples plus filter paper were extracted with 0.125 mol/L NH_4HCO_3 plus 0.05% Tween-20 (vol/vol) for 2 hours at room temperature under constant shaking, with an extraction ratio of 1:10 to 1:100 (wt/vol), depending on the amount of sampled dust. House dust cat allergen *Felis domesticus*

TABLE I. Cat allergen load measured from parents' and children's mattress dust

Sampling site		Fel d 1 (nanogram) Median (25th-75th percentile)
Parents' mattress	Unit/m^2 dust	130.9 (50.9-696)
(N = 2118)	N (detectable %)	88.5%
Children's mattress	Unit/m^2 dust	65.6 (16.6-333.1)
(N = 2098)	N (detectable %)	77.5%

(Fel d) 1 levels were determined using a 2-site monoclonal enzyme-linked immunosorbent assay with 15 ng Fel d 1/g dust detection limit. Endotoxin levels from the same dust extracts were quantified using the kinetic Limulus Amebocyte Lysate assay (Bio Whittaker, Walkerville, Md) with 50 EU/g dust detection limit. Samples under the detection limit were assigned one half of the lower detection limit. The allergen and endotoxin levels were expressed as allergen load, the amount of allergen per meter squared of sample surface. A previous study has shown that microbial level expressed per square meter has a stronger effect on health outcome.[23] In our study, the measured cat allergen level expressed per square meter and per gram dust were highly correlated (Spearman correlation coefficients = 0.9, for both parent and children mattresses). Furthermore, expressing the biocontaminant level in per square meter of the sampling surface simultaneously adjusted the total amount of dust collected.

Statistical analysis

The distribution of cat allergen loads were highly skewed; therefore, they were described using median and quartiles. The correlation between cat allergen loads from parent and children mattresses were calculated using the Spearman correlation coefficient. To describe the associations between cat allergen exposure in infancy and the development of cat sensitization and allergic symptoms and diseases at follow-up, longitudinal analysis with random effects logistic regression models were used. The longitudinal analysis approach takes into account the dependence of repeated outcome measures within each subject. The association between cat allergen exposure and doctor-diagnosed asthma at age 5 and 6 years, however, was calculated using longitudinal analysis with marginal logistic regression model (GEE), because of the small number of children with asthma that caused convergence problems with the random effects model. The confounders adjusted for in the model were selected based on previous literature. The results were presented as odds ratios with 95% CIs for every interquartile range increase in cat allergen exposure. The analyses were performed with proc glimmix procedure, SAS version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Dust samples from 2118 parent mattresses and 2098 children mattresses were available. For those children who slept occasionally in their parents' bed or in their own bed, only the mattress the children had very frequent contact with was sampled. The amount of dust and cat allergen load collected from mattresses is listed in Table I. The estimated correlation between cat allergen loads from parent and children mattresses was 0.6. At age 2 and 6 years, 21 (1.3%) and 43 (5.0%) children, respectively, were sensitized to cat allergen (see Table II for baseline information[24]). In our study, no significant difference was found of the prevalence of cat ownership between the 2 study centers. The prevalence of cat ownership between birth

TABLE II. Baseline information

	n/N (%)
Sensitization to cat at age 2 y	21/1591 (1.3)
Sensitization to cat at age 6 y	43/857 (5.0)
Doctor-diagnosed allergic disease: eczema	
At age 6 mo	128/2047 (6.3)
At age 12 mo	173/1998 (8.7)
At age 18 mo	187/1985 (9.4)
At age 2 y	194/1955 (9.9)
At age 3 y	199/1713 (11.6)
At age 4 y	178/1510 (11.8)
At age 5 y	169/1606 (10.5)
At age 6 y	150/1602 (9.4)
Doctor-diagnosed allergic disease: hay fever	
At age 4 y	33/1655 (2.0)
At age 5 y	44/1604 (2.7)
At age 6 y	66/1599 (4.1)
Doctor-diagnosed allergic disease: asthma	
At age 5 y	16/1660 (1.0)
At age 5 y	35/1603 (2.2)
At age 6 y	33/1603 (2.1)
Study center: Munich	1348/2166 (62.2)
Leipzig	818/2166 (37.8)
Parents had asthma, eczema, or hay fever	1170/2095 (55.8)
Parental education level*: very high	1259/2139 (58.9)
High	385/2139 (18.0)
Median	399/2139 (18.7)
Low	96/2139 (4.5)
Sex: male	1115/2166 (51.5)
Female	1051/2166 (48.5)

*The parental educational level was categorized based on the German educational system, which takes both the highest completed grade in school and the vocational training into account.[24] The higher education level from either parent was taken.

TABLE III. Cat allergen exposure from mattress dust during infancy and cat sensitization rate at age 2 and 6 years

	Adjusted mixed model [OR (CI)]*	
	Parent mattresses	Children mattresses
Cat sensitization at age 2 y†	6.2 (2.6-14.8)	3.7 (1.5-9.1)
Cat sensitization at age 6 y†	1.3 (0.2-9.4)	1.3 (0.2-9.7)
ICC	32%	32%
Reference range of the probability of cat sensitization at baseline (at age 2 y)	1%	2%

*Adjusted for sex, study center, parental educational level, move to another accommodation, and parental allergy (for every interquartile range increase in indoor cat allergen load).
†Specific IgE titer >0.35 kU/L to cat allergen.

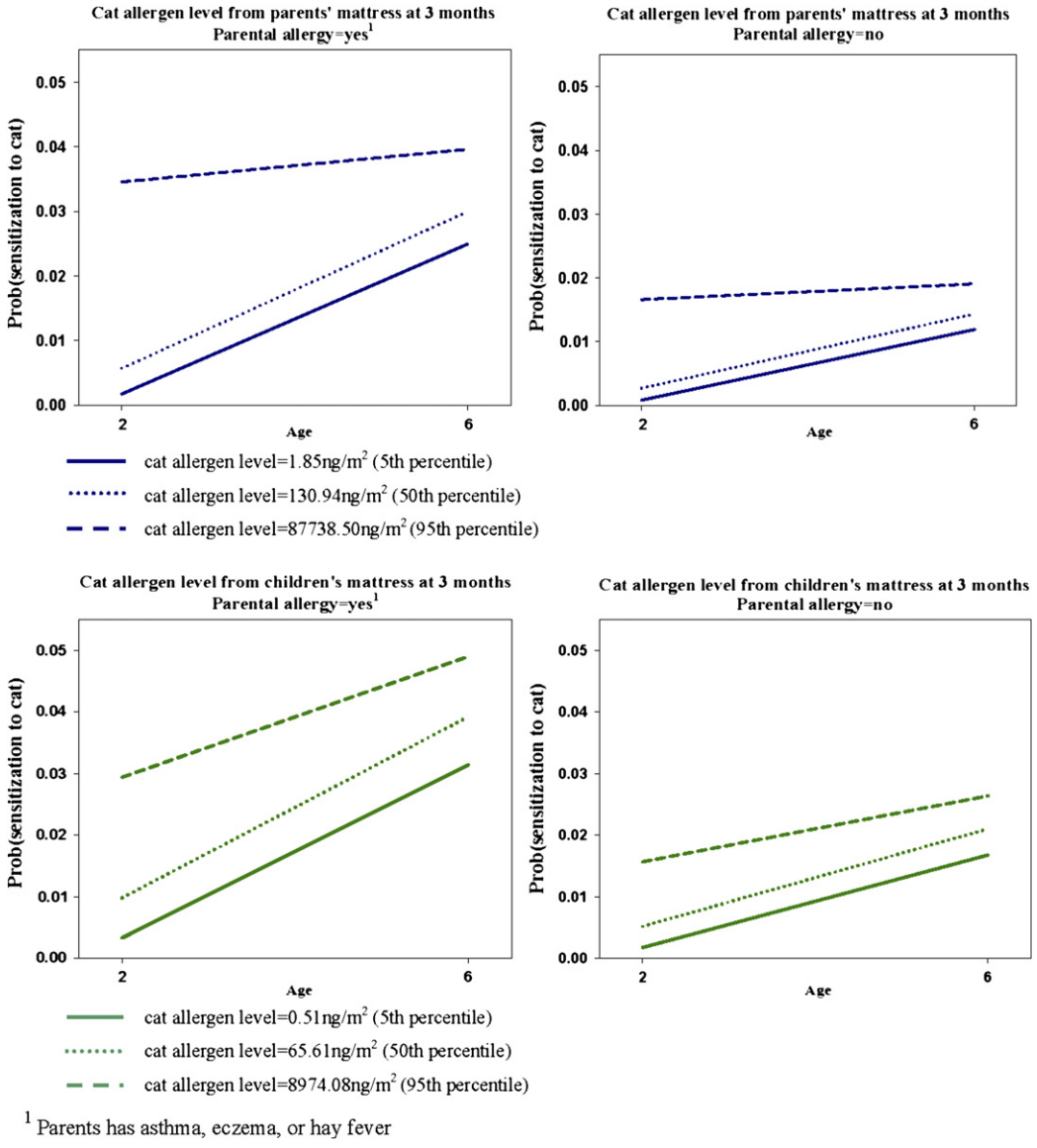

FIG 2. The estimated association between early-life cat allergen exposure from parent and children mattress dust and the cat sensitization rate at age 2 and 6 years.

and age 2 years was 11% in Munich and 12% in Leipzig, and the prevalence between age 2 and 6 years was 12% in Munich and 15% in Leipzig.

The effect of cat allergen exposure in infancy on the development of cat sensitization changed during follow-up. Higher cat allergen exposures from both parent and children mattresses significantly increased the risk of the development of cat sensitization when the children were 2 years old but showed no effect when the children were 6 years old (Table III). The effect of the allergen exposure from parent mattress dust was stronger compared with the effect of the allergen exposure from children mattress dust. The wide interquartile range of cat allergen loads in parent mattress dust compared with children mattress dust also added to the difference between the effect estimates. The intraclass correlation (ICC) was 32% for each model. In other words, 32% of the total conditional outcome variation (the variation of the probability of developing cat sensitization) lies between subjects. Additionally adjusting for endotoxin loads from parent and children mattresses made no change to the associations between cat allergen exposure and cat sensitization development (data not shown).

Fig 2 describes the estimated association between early-life cat allergen exposure from mattress dust and the probability of cat sensitization development at age 2 and 6 years based on the models used in Table III. The figure shows that age and parental history of allergy were

TABLE IV. Cat allergen exposure from mattress dust during infancy and development of allergic diseases and symptoms

	Adjusted mixed model [OR (CI)]*	
	Parents' mattress	Children's mattress
Doctor-diagnosed allergic disease		
Eczema (6, 12, and 18 mo, 2-6 y)	1.0 (0.8, 1.3)	1.0 (0.8, 1.2)
Hay fever (4-6 y)	0.9 (0.5, 1.5)	0.7 (0.4, 1.1)
Asthma (4-6 y)	1.2 (0.7, 2.0)	1.0 (0.7, 1.6)
Symptoms of allergic disease		
Eczema† (6, 12, and 18 mo, 2, 4, and 6 y)	1.0 (0.9, 1.2)	1.0 (0.9, 1.1)
Hay fever‡ (4 and 6 y)	1.2 (0.9, 1.6)	1.1 (0.9, 1.4)
Wheeze‖ (4 and 6 y)	1.2 (0.9, 1.6)	1.1 (0.8, 1.4)

*Adjusted for sex, study centre, parental educational level, move to another accommodation, and parental allergy (for every interquartile range increase in indoor cat allergen load).
†Defined as itchy rash that effected skin crease, face, neck, extremities, hands, or feet.
‡Defined as sneezing, running nose, or nasal congestion without cold.
‖Defined as wheezing sound in the chest.

significant risk factors for the development of cat sensitization during childhood. A very high level of cat allergen exposure in infancy significantly increased the risk of cat sensitization at age 2 years, but the effect weakened as children grew older.

Early-life cat allergen exposure from mattress dust had no effect on the development of allergic symptoms and diseases during childhood (Table IV). Furthermore, the associations between cat allergen exposure in infancy and the development of allergic symptoms and diseases were constant over the follow-up period. Our data showed that cat allergen exposure in infancy induced the development of cat sensitization in early childhood, but it did not directly increase the risk of the development of allergic symptoms and diseases up to age 6 years.

Using family cat ownership during the first 6 years and regular cat contact during the first 4 years of life as surrogates of continuous cat allergen exposure during childhood, we analyzed its effect on the development of cat sensitization. Both cat ownership and regular cat contact without ownership increased the risk of sensitization to cat during childhood (at both age 2 and 6 years) (Table V). Unlike the effect of early-life cat allergen exposure from mattress dust, the effect of cat ownership and regular cat contact during childhood on the development of cat sensitization was consistent over the follow-up period. However, previous cohort study in Sweden has shown a strong negative association between maternal pet allergy and pet ownership.[14] To overcome possible bias from selective avoidance of cats by children with parental history of allergy, a stratified analysis was performed. We stratified the cohort by the family history of allergic disease and reanalyzed the association between cat sensitization rate and cat ownership and regular cat contact. The results showed that regular cat contact was positively associated with a higher risk of cat sensitization during childhood (at both age 2 and 6 years) only for those children whose parents had asthma, eczema, or hay fever. For children whose parents never had allergic disease, cat contact only during childhood was not a risk factor for the development of sensitization. Cat ownership, however, was associated with the development of cat sensitization for children from families with or without history of allergic disease at a 10% significance level (Table V). The high ICC suggested that unknown factors during childhood still determine the progressive development of sensitization in each individual. These individual differences in the probability of sensitization development in early childhood were more pronounced among the children whose parents had asthma, eczema, or hay fever.

The main difficulty in a longitudinal cohort study is the withdrawals and losses of the participants during the follow-up period. In our study, only half of the children had their blood examined again at age 6 years. We therefore performed sensitivity analysis. The results showed that the estimated association between cat allergen exposure in infancy and the development of cat sensitization at age 2 years did not differ between the whole study cohort ($n = 1591$) and for those who have been followed up to age 6 years ($n = 857$) (data not shown).

Furthermore, in the study, not all children who have been followed up agreed to participate in the blood examination. At year 6 years, only 50% of the followed-up children had their blood sampled. We therefore compared the demographic characteristics between children with and without IgE measurements (Table VI). We found that parents with higher educational levels are more willing to let their children participate in the IgE measurement. A lower proportion of the children who have moved between birth and age 6 years had their blood sampled than the nonmovers. Parental allergic disease, however, was not associated with the participation of the IgE measurement. We also assessed whether doctor-diagnosed allergic disease or allergic symptoms were associated with the willingness of participation. In the Munich subgroup, slightly more children who have been found to have asthma at age 6 years participated in the IgE measurement at age 6 (55% vs 51%). Differences between participation rates of children whose parents reported and did not report allergic symptoms in the questionnaire were between 0% and 9%. None of the differences between the participation rates was statistically significant except in the Munich subgroup; those who reported hay fever symptoms at age 6 years were more likely to participate in the IgE measurement at age 6 years (59% vs 50%, χ^2 test; $P = .03$).

DISCUSSION

Our results showed a positive association between cat allergen exposure during infancy and the sensitization rate up to age 2 years but not at age 6 years. No associations existed between cat allergen exposure in

TABLE V. Cat ownership and regular cat contact during childhood and the cat sensitization rate at age 2 and 6 years

	Adjusted mixed model [OR (CI)]†	
	Cat ownership	**Cat contact only‡**
Cat sensitization*	2.4 (1.2-4.7)	2.4 (1.3-4.5)
ICC	33%	32%
Reference range of the probability of cat sensitization at baseline (at age 2 y)	6%	9%

	Stratified analysis by parental allergy			
	Parental allergy = yes (n = 925)		**Parental allergy = no (n = 1170)**	
	Cat ownership (n = 156)‖	**Cat contact‡ (n = 422)§**	**Cat ownership (n = 167)‖**	**Cat contact‡ (n = 317)§**
Cat sensitization*	2.24 (0.91, 5.51)	2.76 (1.28, 5.95)	2.38 (0.85, 6.66)	1.51 (0.44, 5.22)
ICC	37%	35%	5%	9%
Reference range of the probability of cat sensitization at baseline (at age 2 y)	8%	8%	3%	2%

*Specific IgE titer >0.35kU/L to cat allergen.
†Adjusted for sex, study center, and parental educational level.
‡Cat owners were excluded.
‖Ever had a cat as pet between birth and age 6 years.
§Ever had regular contact with cat between birth and age 4 years.

TABLE VI. Demographic characteristics between children with and without IgE measurements by study center

	Munich, n/N (%)		Leipzig, n/N (%)	
IgE measurement	**At age 2 y**	**At age 6 y**	**At age 2 y**	**At age 6 y**
Parents had asthma, eczema, or hay fever				
Yes	627/820 (76)	357/820 (44)	265/350 (76)	131/350 (37)
No	359/499 (72)	199/499 (40)	302/426 (71)	153/426 (36)
Parental education level*				
Very high	681/903 (75)‡	402/903 (45)‡	274/356 (77)‡	142/356 (40)‡
High	173/217 (80)	88/217 (41)	129/168 (77)	64/168 (38)
Median and low	143/215 (67)	71/215 (33)	183/280 (65)	84/280 (30)
Move in the first 2/6 y†				
Yes	276/358 (77)	258/570 (45)‡	213/277 (77)‡	144/379 (38)‡
No	720/898 (80)	302/581 (52)	358/431 (83)	143/226 (63)

*The parental educational level was categorized based on the German educational system, which takes both the highest completed grade in school and vocational training into account.[24] The higher education level from either parent was taken.
†The association between IgE measurement at age 2 years and move in the first 2 years of life and the association between IgE measurement at age 6 years and move in the first 6 years of life were assessed.
‡χ^2 test, P value less than .05.

infancy and allergic symptoms and diseases up to age 6 years. Cumulative allergen exposure from cat ownership and regular cat contact outside the domestic area during childhood was found to increase the risk of cat sensitization development at school age. The results also confirmed that age and family history of allergic disease are risk factors for the development of sensitization.

The major difficulty in the interpretation of our results is that cat allergen is ubiquitous and none of the pet allergen exposure study can precisely measure the overall allergen exposure of each individual, particularly if the child also spends time in an indoor environment other than the family home such as a daycare center or relative's home. In our study, we used the Fel d 1 levels in mattress at age 3 months as a surrogate of cat allergen exposure in infancy. Although infants tend to spend most of their time in bed, they may also be exposed to different levels of cat allergen on other furniture, carpet, in the air, or even outdoors. Furthermore, the allergen level may change dramatically once the family gets a cat or moves to another accommodation where a cat used to live. Similarly, cat ownership and cat contact are also not the precise index of cat allergen exposure during childhood. Finally, as in every longitudinal cohort study, we lost participants during the follow-up, and some participated in the IgE test at age 2 years but did not participate in the IgE test at age 6 years. We do not think that selective participation can explain the study results because the sensitivity analysis showed that predisposed children and children

with allergic disease or symptoms did not have a much higher participation rate. However, the results must be interpreted with caution.

In our study, high cat allergen exposure during infancy significantly increased the risk of cat sensitization at age 2, but the effect weakened when the time lag between exposure and health outcome became bigger. The German Multicentre Allergy Study has reported that cat allergen exposure during the first 2 years of life correlates with cat sensitization at 5 and 7 years but not 10 years.[2] For older children, domestic cat allergen is no longer the major source of exposure to cat allergen and exposure from community, school, and regular contact with cat from their friends and relatives may be more important for the later cat sensitization development.[25,26] We also found increased risk of cat sensitization development in children who had regular cat contact but were not cat owners, particularly in the subgroup of children whose parents had asthma, eczema, or hay fever. Cumulative passive cat allergen exposure in later childhood may also partly explain the higher sensitization rate at preschool and school age. It should be acknowledged that sensitization is not a clinical symptom and our study cohort was still too young to assess the effect of cat allergen exposure on the development of allergic diseases. However, it has been reported by the large-scale cohort study that sensitization to perennial inhalant allergens in early childhood is highly associated with loss of lung function at school age.[17] Therefore, our study results could be interpreted as the initiation of allergic disease development, as subjects with allergy sensitization are at a higher risk of developing allergic disease.

Contradictory results in the association between cat allergen exposure and cat sensitization rate have also been reported. Several cross-sectional studies have suggested that a high level of cat allergen exposure is negatively associated with sensitization development.[27,28] This protective effect may be from the modified T_H2 response that corresponds to the production of IgG_4 antibodies but not IgE when in contact with cat allergen.[8] However, no direct evidence shows that IgG_4 antibodies directly mediate a protective effect.[2,27] The observed phenomena in cross-sectional studies can also be explained by the selective avoidance effect.[14,29] In our study, the level of cat allergen concentration in the house dust samples was much lower than the sampled allergen concentration in the studies by Platts-Mills et al[8] and Custovic et al.[30] Therefore, the dose of exposure might not be sufficient for the induction of the immune tolerance suggested by Platts-Mills et al.[8] However, in our study, cat ownership was associated with the development of cat sensitization for children from families with or without history of allergic disease. This result was a strong indication that even a very high amount of cat allergen exposure is a risk factor for the development of cat sensitization, and no evidence of the induction of immune tolerance was observed in our study. It was also suggested that pet keeping may increase the indoor bacterial components such as endotoxin[11] which may downregulate the type 2 immune response.[13] However, our study showed that additional adjustment for endotoxin in domestic dust did not modify the associations between cat allergen exposure and cat sensitization.

For practical and economic reasons, we could not monitor allergen levels in our cohort's household over 6 years and had to use cat ownership and regular cat contact to approximate the allergen exposure during childhood, although pet ownership has been considered as a poor surrogate for the specific allergen exposure.[31-33] Sensitivity analysis showed that cat ownership and regular cat contact outside the residence at age of 3 months and in the first 2 years of age statistically significantly increased the risk of cat sensitization at age 2 years. This finding was in line with the positive association between cat allergen exposure in infancy and cat sensitization rate in early childhood. On the other hand, the Dutch Prevention and Incidence of Asthma and Mite Allergy study has shown that domestic cat allergen loads can be considered very stable over more than 4 years, as the ratio of within-home to between-home variances is always below unity[34]; therefore, the domestic cat allergen load collected when the children were 3 months old may be considered as an appropriate measurement for the exposure during early childhood.

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